UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/391,606 | 09/07/1999 | ANDREW D. MURDIN | 1038-971-MIS | 8817 |

7590 02/22/2002

SIM & MCBURNEY
330 UNIVERSITY AVENUE
6TH FLOOR
TORONTO, M5G1R7
CANADA

| EXAMINER |
|---|
| CHEN, SHIN LIN |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 02/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/391,606 | MURDIN ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7 and 9-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

It should be noted that the examiner for the present application has been changed, any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen.

Applicants' amendment filed 12-5-01 has been entered. Claim 1 has been amended. Claims 21-23 have been canceled. Claims 1-20 are pending and claims 1, 2, 4-7 and 9-20 are under consideration.

Since SEQ ID Nos. 1-16 are directed to two genes, i.e. MOMP and 76 kDa genes, and both genes are recited in the claims, therefore SEQ ID Nos. 1-16 are examined in the present application.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 10, 11, 14 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "encodes a 76 kDa protein having a molecular size of about 35 kDa" in claim 10 is vague and renders the claim indefinite. It is unclear how a 76 kDa protein also has a

molecular size of 35 kDa. It is unclear whether the nucleotide sequence encodes a 76 kDa protein or a 35 kDa protein.

The phrase "encodes a 76 kDa protein having a molecular size of about 60 kDa" in claim 11 is vague and renders the claim indefinite. It is unclear how a 76 kDa protein also has a molecular size of 60 kDa. It is unclear whether the nucleotide sequence encodes a 76 kDa protein or a 60 kDa protein.

The phrase "plasmid vector has the identifying characteristics of pCAMOMP as seen in Figure 4" in claim 14 is vague and renders the claim indefinite. It is unclear what are the "identifying characteristics of pCAMOMP". The specification fails to specifically define "identifying characteristics of pCAMOMP".

The phrase "plasmid vector has the identifying characteristics of pCA76kDa as seen in Figure 2" in claim 16 is vague and renders the claim indefinite. It is unclear what are the "identifying characteristics of pCA76kDa". The specification fails to specifically define "identifying characteristics of pCA76kDa".

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 4-7, 9-17, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on nucleotide sequence encoding any major outer membrane protein (MOMP) of any strain of Chlamydia and/or nucleotide sequence encoding any 76 kDa protein of any strain of Chlamydia. The genus of *Chlamydia* includes different species *C. Pneumoniae*, *C. Psittaci*, and *C. Trachomatis*. Each species of *Chlamydia* encompasses numerous different strains that have different host range, virulence, pathologies, and antigen composition. The specification of the present application only discloses nucleotide sequence encoding MOMP (SEQ ID No. 1) or 76 kDa protein (SEQ ID No. 12) of a strain of *C. Pneumoniae.*

The scope of the claim includes nucleotide sequences encoding a genus of numerous structural variants of the disclosed MOMP or 76 kDa protein, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the nucleotide sequences encoding those MOMP or 76 kDa proteins derived from various species and strains of *Chlamydia.* Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or

characteristics that identify members of the genus, and because the genus is highly variant, the nucleotide sequence encoding MOMP (SEQ ID No. 1) or 76 kDa protein (SEQ ID No. 12) of a strain of *C. Pneumoniae* is insufficient to describe the genus.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the nucleotide sequences encoding MOMP or 76 kDa proteins derived from various species and strains of *Chlamydia* for the immunogenic composition as claimed. Thus it is concluded that the written description requirement is not satisfied for the nucleotide sequences encoding the genus of structural variants of MOMP or 76 kDa protein disclosed for the claimed immunogenic composition.

5. Claims 1, 2, 4-7 and 9-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of a plasmid encoding the disclosed MOMP and a plasmid encoding the disclosed 76 kDa of *C. Pneumoniae* before challenge of *C. Pneumoniae*, and induction of a protective immune response against sublethal *C. Pneumoniae* lung infection in mice, does not reasonably provide enablement for an immunogenic composition comprising a vector encoding any MOMP and/or 76 kDa protein derived from any species or any strain of *Chlamydia* for the protection of any host, including human, against a particular disease, such as any chlamydial infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 2, 4-7 and 9-20 are directed to an immunogenic composition for in vivo administration to a host comprising a first vector comprising a nucleotide sequence encoding a MOMP of a strain of *Chlamydia*, such as a strain of *Chlamydia pneumoniae*, and a second vector having nucleotide sequence encoding a 76 kDa protein of a strain of *Chlamydia*, such as a strain of *Chlamydia pneumoniae*, and a pharmaceutical acceptable carrier. The claims further specify the nucleotide sequence having any one of SEQ ID Nos. 1-4 and 12-14, or specify the nucleotide sequence encoding any one of SEQ ID Nos. 7-9, 15 and 16. SEQ ID Nos. 2-4 and 7-9 are fragments of SEQ ID No. 1 or fragment of the amino acid sequence encoded by SEQ ID No. 1. SEQ ID Nos. 13, 14 are fragments of SEQ ID No. 12, and SEQ ID No. 16 is fragment of SEQ ID No. 15.

The claims read on using nucleotide sequence encoding any MOMP and/or 76 kDa protein derived from any species or any strain of *Chlamydia* for *in vivo* administration of any host, including human, mammals, birds, reptiles, fishes etc., to protect the host against a particular disease. The claimed immunogenic composition comprising the nucleotide sequence set forth above administered *in vivo* to a host must have a use for one skilled in the art at the time of the invention. The specification only discloses the use of a vector (pCAMOMP) expressing MOMP and a vector (pCA76kDa) expressing a 76 kDa protein of a strain of *C. Pneumoniae* as disclosed in the present application for protection against *C. Pneumoniae* lung infection in mice. The specification fails to provide adequate guidance and evidence for an immunogenic composition containing nucleotide sequences encoding any MOMP and/or 76 kDa protein

derived from any species or any strain of *Chlamydia* for *in vivo* administration of any host, including human, mammals, birds, reptiles, fishes etc., to protect the host against a particular disease.

The nucleotide sequences encoding various MOMPs or 76 kDa proteins of strains of *Chlamydia* could vary dramatically from the nucleotide sequence of SEQ ID No. 1 and SEQ ID No. 12 disclosed in the present application, and the protein sequences encoded by said nucleotide sequence could vary dramatically from the amino acid sequences of the disclosed MOMP and 76 kDa protein. The structural features within MOMP or 76 kDa protein of Chlamydia that contributes to the protection of a host from chlamydial infection has not been disclosed. It is unclear whether MOMPs and 76 kDa proteins derived from various strains of Chlamydia also could provide protection of any host against any chlamydial infection. It was known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma

protein defective in phosphorylation and oncoprotein binding" (e.g. Title). It was unpredictable to determine a protein function from mere amino acid sequence. Determination of whether MOMPs and 76 kDa proteins derived from various strains of *Chlamydia* could provide protection of any host against any chlamydial infection would require undue experimentation to practice over the full scope of the claimed invention.

The claims also read on gene therapy *in vivo* because of the *in vivo* administration to a host of the immunogenic composition comprising vectors expressing MOMP and/or 76 kDa protein is to protect said host from any particular disease, such as chlamydial infection. The specification only discloses the use of a vector (pCAMOMP) expressing MOMP and a vector (pCA76kDa) expressing a 76 kDa protein of a strain of *C. Pneumoniae* as disclosed in the present application for protection against *C. Pneumoniae* lung infection in mice. The specification fails to provide adequate guidance and evidence for protection of any host, including humans, against a particular disease, such as chlamydial infection, via administration of an immunogenic composition comprising vectors expressing MOMP and/or 76 kDa protein derived from any strain of chlamydia.

While progress has been made in recent years related to in vivo gene transfer, the filed of in vivo gene transfer at the time of the invention was unpredictable as exemplified in Anderson's review of the state of the art of gene therapy (Anderson, Nature, 1998, Vol. 392, p. 25-30). The unpredictability can be attributed to several factors including "...poor delivery systems, both viral and non-viral, and poor gene expression after gene are delivered...we still lack a basic

understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make" (e.g. p. 30). Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, McGraw-Hill, New York, p. 77-101) explains that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA are all important factors for successful gene transfer *in vivo*.

Furthermore, with regard to extrapolation from mouse models to man, the state of the art exemplified by McCluskie et al., 1999 (Molecular Medicine, Vol. 5, p. 287-300) teaches that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in non-human primates...IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees...and essentially not all in Aotus monkeys" and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (e.g. p. 296, column 2, second and third paragraph). McCluskie also teaches that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the

requirement to transfer cells and express the antigen, relies on many factors other than immunological responses to the antigen" (p. 297, column 1).

Moreover, Stagg et al., 1998 (Molecular Medicine Today, April 1998, p. 166-173) teaches that "the immune response to Chlamydia is both complex and flexible...it is not yet clear which is the most appropriate response to target for immunoprophylaxis, or whether it will be possible to confer protection while avoiding immunopathology. Much of our understanding of cell-mediated immunity in chlamydial infection is based upon mouse models; little is known about the response in humans. Given that the infection in humans runs a chronic course and appears to produce only short-term, serovar-specific immunity, the possibility that the organism has evolved mechanisms to block or evade the protective mechanisms that have been identified in mice warrants further investigation. A vaccine aimed at reducing the damage associated with severe disease might be a more realizable goal than one aimed at preventing infection" (p. 169, left column). Accordingly, the state of the art regarding chlamydia vaccines at the time of the invention was unpredictable. The mechanisms involved in the immune response vary greatly depending on the antigen at issue. One skilled in the art at the time of the invention would recognized that the results obtained in the mouse model as described are not necessarily predictive of the outcome in other species of animals, including humans, particularly in light of the teachings of Stagg.

In addition, the specification also fails to provide adequate guidance and evidence for the use of the claimed immunogenic composition in protecting or treating disease or disorder other

than chlamydial infection. Different diseases or disorders vary dramatically pathologically. It is unclear how the claimed immunogenic compositions can protect any host from or treat any disease or disorder other than chlamydial infection via various *in vivo* administration routes to said host.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention to engage in undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the claimed immunogenic composition shows protection in mice against intranasal challenge by *C. pneumoniae* (amendment, page 3). This is not found persuasive because of the reasons set forth above.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.